Clinical Policy Title: Immunotherapies for prostate cancer and acute lymphoblastic leukemia

Clinical Policy Number: 05.02.04

Effective Date: March 1, 2015
Initial Review Date: October 15, 2014
Most Recent Review Date: October 19, 2016
Next Review Date: October 2017

Policy contains:
- Sipuleucel-T (Provenge) for prostate cancer.
- Blinatumomab (Blincyto®) for acute lymphoblastic leukemia.
- Monoclonal antibodies and vaccines.

Related policies:
None.

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Prestige Health Choice when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Prestige Health Choice’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

Prestige Health Choice considers autologous cellular immunotherapy, (i.e., Sipuleucel-T (Provenge) for prostate cancer to be clinically proven and, therefore, medically necessary when the following criteria are met:

- Castration-resistant metastatic prostate cancer is documented.
- Patient is asymptomatic or minimally symptomatic.
- (Eastern Cooperative Oncology Group) performance status 0-1 exists.
- No visceral metastasis, or liver metastasis, exists.
- Prior therapy (docetaxel) has been attempted.
- Life expectancy is greater than three months.

Prestige Health Choice considers intravenous immunotherapy (i.e., blinatumomab [Blincyto®]) to be clinically proven and, therefore, medically necessary for treating B-cell precursor acute lymphoblastic leukemia.
leukemia (ALL) to be clinically proven and, therefore, medically necessary when all of the following criteria are met:

- The disease is Philadelphia chromosome-negative B-cell precursor to ALL
- The disease is Philadelphia chromosome-negative B-cell ALL that is refractory to tyrosine kinase inhibitor therapy.
- The disease if relapsed or refractory to other treatment
- Blinatumomab will be used as monotherapy.
- Dose does not exceed 28 mcg/day

**Limitations:**

Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website can be accessed at http://ahca.myflorida.com/Medicaid/.

All other uses of sipuleucel-T (Provenge) and blinatumomab (Blincyto) are not medically necessary.

**Alternative covered services:**

Hormonally insensitive prostate cancer may be treated with alternative medications, including chemotherapy (i.e., cyclophosphamide) or antiandrogenic agents (i.e., flutamide). ALL may be treated by chemotherapeutic multidrug regimens administered in a sequential plan over two to three years.

**Background**

Immunotherapy is a broad classification, including monoclonal antibodies and vaccines, referring to therapeutic uses for modifications, priming, enhancing or directing normal immune responses to disease. Antibodies are products of the immune system directed against infectious agents (microbes) or other cells recognized by the host as “foreign,” including cancer cells, some of which have distinct cell-surface or cell-membrane characteristics recognizable by the immune system. Monoclonal antibodies (mAb) are identical chemical structures because the antibodies are produced by a clone of cells all originating in the same parent cell.

MAbs are produced in the laboratory or commercially by hybridoma technology, which fuses human cancer cells with spleen cells from a mouse immunized with the antigen or foreign substance against which the mAb will be directed. The fused cells are then cultured and handled with specialized laboratory techniques to produce the quantity of mAb needed. MAb applications include diagnostic tests and therapeutic agents for immune-mediated diseases, such as rheumatoid arthritis, ulcerative colitis and cancer.

Sipuleucel-T is a treatment for asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer approved by the FDA in April, 2010 – the only immunotherapy for this disorder. Prior to its
development, the only treatment for these indications was docetaxel. The promise of Sipuleucel-T, created from the patient’s white blood cells, is to stimulate the immune system to target cancer cells.

Trials employed a minimum of 40 million cells for each dose. They showed an increased survival and adverse events that rarely caused the patient to be hospitalized. However, trials could not determine quality of life indicators, potential confounding effects of subsequent treatments, and whether post-progression chemotherapy interacted positively or negatively with Sipuleucel-T (AHRQ, 2011).

Blinatumomab (Blincyto™) is the first bispecific T-cell engager (BiTE) Immunotherapy product to be approved by the FDA, in December 2014, for the treatment of Philadelphia chromosome-negative, relapsed, or refractory B-cell precursor ALL. It creates a bridge between the T-cell and the cancer cell, by binding to two different proteins at the same time (CD19 located on malignant B-cells and CD3 located on T-cells); this triggers activation of the T-cells which ultimately will cause the death of the malignant cells.

This rare type of blood cancer originates in the bone marrow, where blood cells are formed, and results in the overproduction of cancerous, immature white blood cells. Prior to FDA approval, the drug was shown to eliminate residual disease in 80% of patients with relapsed or MRD-positive B-precursor ALL after intensive chemotherapy (FDA, 2014).

**Searches**

Prestige Health Choice searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on September 13, 2016. Searched terms were: “blintumomab” and "sipuleucel."

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

Guidelines for use of immunotherapy for acute lymphoblastic leukemia and prostate cancer are given in two separate clinical guidelines from the National Comprehensive Care Network (NCCN, 2016a and 2016b).
A Phase III trial of 512 men with metastatic castration-resistant prostate cancer were either given Sipuleucel-T administrations (n=341) or placebo (n=171). A 22% reduction in mortality was found in the treatment group, and 36 month survival was greater than placebo (31.7 vs. 23.0) (Kantoff, 2010). A similar study of 512 patients documented similar results (Schellhammer, 2013).

One systematic review compared 737 asymptomatic/minimally symptomatic patients receiving Sipuleucel-T to those receiving docetaxel-based chemotherapy for safety and efficacy. The survival rate was 27% greater for the Sipuleucel-T group, insignificant differences were found for time to disease progression, relative benefit of serum PSA levels, and relative risks – overall grade 3 to 5, and cerebrovascular – were documented (Kawalec, 2012). One assessment of three studies of Sipuleucel-T and placebo (comparator of antigen-presenting cells) found significantly greater survival rates for Sipuleucel-T. There was no difference between groups in the time to disease progression. Most adverse events occurred the first day and resolved by the second day (Simpson, 2015). Another systematic review of 26 studies found that median overall survival for chemotherapy-naïve patients on Sipuleucel-T was 26 months, which the authors call “an improvement in the postdocetaxel setting” (Seal, 2013).

Another recent article assessed 25 publications that reviewed seven modalities of treatment for metastatic castration-resistant prostate cancer. Sipuleucel-T was one of the four modalities that offered varying levels of improved quality of life and/or pain mitigation; the other three were abiraterone acetate and prednisone; enzalutamide; and radium-223 dichloride. Those showing no meaningful impact were mitoxantrone, estramustine phosphate and docetaxel, and cabazitaxel (Nussbaum, 2016).

Blinatumomab (Blincyto), a treatment for ALL targeting the CD19 antigen found in B cells, is administered as a continuous intravenous infusion via an infusion pump. A cycle of treatment consists of four weeks of continuous infusion; hospitalization is recommended for the first nine days of the first cycle and the first two days of the second cycle. Each cycle of treatment is followed by a two-week treatment-free interval.

The FDA approval for blinatumomab is based on the results of the MT103-211 trial, a phase II, multicenter, single-arm study that evaluated the therapy in 185 patients (Topp, 2014). Sixty patients (32.4%) achieved complete remission with full recovery of peripheral blood counts within the first two treatment cycles, and another 17 patients (9.2%) achieved complete remission with partial recovery of peripheral blood counts. The majority of responses (81%) occurred within the first cycle of treatment.

In trials, blinatumomab showed to eliminate residual disease in 80% of patients with relapsed or MRD-positive B-precursor ALL after intensive chemotherapy (FDA, 2014). The treatment was later associated with a 67% response rate in patients with relapsed/refractory B-precursor ALL (Topp, 2011b). Another study showed a 61% hematological survival rate after 33 months (Topp, 2014). However, side effects from the drug are not uncommon, especially in the first days after administration, including neurotoxicities (50%) and cytokine release syndrome (FDA, 2015).
Of 36 adults with relapsed/refractory ALL followed for several years on blinatumomab, 10 were long term survivors of 30 months or more, with the median survival of 13 mont, and a median Relapse Free Survival of 8.8 months (Zugmaier, 2015).

In a recent study of 36 elderly and 225 non-elderly adults, blinatumomab achieved complete remission in 56% of the elderly within four weeks, compared to just 46% for non-elderly. Older subjects had a similar rate of grade three or greater adverse events (86% vs. 80%), but a higher rate of grade three or greater neurologic events (28% vs. 13%). No fatalities were reported (Kantarjian, 2016).

**Policy Updates:**

The 2016 version of this policy is focused only on immunotherapy for prostate cancer and for acute lymphoblastic leukemia, and not those for other malignancies. The new title reflects this change. A total of 7 additional guidelines/related sources, plus 15 new peer-reviewed references have been added.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Method, Recommendations</th>
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<tbody>
<tr>
<td><strong>Kantarjian (2016)</strong></td>
<td>Key points:</td>
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</tbody>
</table>
| Ability of blinatumomab to achieve remission in elderly patients with ALL | - Elderly (n=36) and non-elderly (n=225) patients with ALL receiving blinatumomab  
  - 56% of elderly and 46% of non-elderly achieved complete remission  
  - Elderly had slightly more grade three or more adverse events (86% vs. 80%)  
  - Elderly had significantly more grade three or more neurologic events (28% vs. 13%)  |
| **Topp (2015)**     | Key points:                      |
| Ability of blinatumomab to achieve hematologic remission in ALL patients | - Single-agent blinatumomab showed antileukaemia activity in adults with relapsed or refractory ALL characterized by negative prognostic factors (n=189)  
  - 43% achieved complete or partial hematologic remission.  
  - Common adverse events were febrile neutropenia (25%), neutropenia (16%), anemia (14%).  |
| **Small (2014)**    | Key points:                      |
| Sipuleucel-T and survival in men with castration-resistant metastatic prostate cancer | - Sipuleucel-T has demonstrated improved overall survival.  
  - Sipuleucel-T is associated with longer time to first use of opiate drugs for pain control.  
  - There is evidence of a delayed treatment effect, consistent with an active immunotherapy.  |
| **Kawalec (2012)** | Key points:                      |
| Safety and efficacy of Sipuleucel-T treatment in prostate cancer | - Systematic review of three trials (n=737), comparing Sipuleucel-T and docetaxel  
  - Survival 27% greater for Sipuleucel-T group  
  - Insufficient differences between groups found from time to disease progression, relative benefit of serum PSA, and relative risks for treatment group not significantly different than |
<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Method, Recommendations</th>
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<tbody>
<tr>
<td>Beer (2011)</td>
<td>Post-surgical prostate cancer patients receiving Sipuleucel-T vs. controls</td>
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<td>Key points:</td>
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<tr>
<td></td>
<td>- Randomized Controlled Trial, 117 with Sipuleucel, 59 controls</td>
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<td></td>
<td>- Main measure was time to biochemical failure (BF)</td>
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<tr>
<td></td>
<td>- Median months to BF was not significantly higher for Sipuleucel (18.0 vs. 15.4 controls.</td>
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<tr>
<td>Adams (2010)</td>
<td>Sipuleucel-T as a treatment for castration-resistant metastatic prostate cancer</td>
</tr>
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<td>Key points:</td>
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<tr>
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<td>- FDA-approved, but benefits limited to asymptomatic/minimally symptomatic prostate cancer</td>
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<td>- Sipuleucel-T is not an off-the-shelf drug, need for specialized labs may restrict access.</td>
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<td></td>
<td>- Effectiveness data for Sipuleucel-T are confounded by inconsistencies in treatment regimens (i.e., concomitant use of docetaxel).</td>
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<tr>
<td>Kantoff (2010)</td>
<td>Reduction in mortality among men with prostate cancer after administration of Sipuleucel-T</td>
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<td>Key points:</td>
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<td>- RCT of 512 men, 341 given Sipuleucel-T and 171 placebo</td>
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<td></td>
<td>- Sipuleucel-T group had 22% lower death rate after 3 infusions every 2 weeks</td>
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<td>- 36 month survival was 31.7% and 23.0% for Sipuleucel-T and control groups</td>
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**Glossary**

**Blinatumomab (Blincyto)** – An immunotherapy treatment for Philadelphia chromosome-negative relapsed or refractory acute lymphoblastic leukemia, which target the CD19 antigen found in B.

**Immunotherapy** – Therapeutic uses for modifications, priming, enhancing, or directing normal immune responses to disease.

**Sipuleucel-T (Provenge)** – A vaccine treatment for asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer that stimulates the immune system to target cancer cells.

**References**

**Professional society guidelines/other:**


American Cancer Society. Monoclonal Antibodies to Treat Acute Lymphocytic Leukemia. 


http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/125557Orig1s00ltr.pdf.


**Peer-reviewed references:**


Seal BS, Asche CV, Puto K, Allen PD. Efficacy, patient-reported outcomes (PROs), and tolerability of the changing therapeutic landscape in patients with metastatic prostate cancer (MPC); a systematic literature review. Value Health. 2013;16(5):872–90.


**Clinical trials:**

Searched clinicaltrials.gov on September 13, 2016 using terms “blinatumomab” and “sipuleucel .” | Open Studies. 16 studies found, two (2) relevant (blinatumomab); 14 studies found, two (2) relevant (sipuleucel).


**CMS National Coverage Determination (NCDs):**


**Local Coverage Determination (LCDs):**
A52422 Autologous Cellular Immunotherapy Treatment of Metastatic Prostate Cancer.  

**Commonly Submitted Codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<th>CPT Code</th>
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<table>
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<tr>
<th>ICD-10 Code</th>
<th>Description</th>
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<tr>
<td>C61</td>
<td>Malignant neoplasm of prostate</td>
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<tr>
<td>C91.00</td>
<td>Acute lymphoblastic leukemia not having achieved remission</td>
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<tr>
<td>C91.02</td>
<td>Acute lymphoblastic leukemia, in relapse</td>
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<tr>
<th>HCPCS Level II</th>
<th>Description</th>
<th>Comment</th>
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<tbody>
<tr>
<td>J9039</td>
<td>Injection, blinatumomab, 1 mcg</td>
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<tr>
<td>Q2043</td>
<td>Sipuleucel-T, minimum of 50 million autologous cd54+ cells activated with PAP-GM-CSF, including leukapheresis and all other preparatory procedures including infusion.</td>
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<tr>
<td>S2107</td>
<td>Adoptive immunotherapy i.e. development of specific antitumor reactivity (e.g., tumor-infiltrating lymphocyte therapy) per course of treatment</td>
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